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JAK Inhibition in the Aicardi-Goutières Syndrome

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First, we found that the incidence of atypical femur fracture was unrelated to BMD and only weakly related to age. Second, when we performed a subgroup analysis in the Kaiser Permanente cohort that was limited to women who were older than 65 years of age and who had a BMD T-score of less than –2.5, we found an incidence of atypical femur fracture similar to the incidence in the overall cohort (unpublished data). The correspondents question whether we overestimated the fracture benefit of 5 to 10 years of alendronate, since the FLEX trial[1] and observational data[2] showed no increase in the risk of clinical fracture after alendronate was discontinued after 5 years. However, studies involving patients with 5 years of previous treatment are not relevant, since our estimate of the fractures that were prevented with alendronate was based on a comparison of women who were never treated with those who were continuously treated. We agree that our findings that show large decreases in the risk of atypical femur fracture after the discontinuation of alendronate provide support for a drug holiday after 5 years, particularly for women at lower risk.

Garton questions whether an underestimation of the incidence of atypical femur fracture biases the ratio of such fractures to fragility fractures. However, we think that our adjudication, starting with all femoral-shaft or subtrochanteric fractures, identified virtually all complete unilateral and bilateral atypical femur fractures. However, incomplete fractures would not have been included unless they had been prophylactically repaired. We agree that accumulating microdamage is part of the pathophysiology of atypical femur fracture, but its effect on only a small minority of patients remains unexplained.[3] Regarding the consequences of atypical femur fracture as compared with hip fracture, several studies have suggested similar mortality[4] after either type of fracture, although surgical repair of atypical femur fractures can be more challenging.[3]

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Since publication of their article, the authors report no further potential conflict of interest.

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JAK Inhibition in the Aicardi–Goutières Syndrome

TO THE EDITOR: Some reports,[1-3] including that of Vanderver et al. (Sept. 3 issue),[4] have indicated the potential of Janus kinase 1 (JAK1) blockade in the treatment of type I interferonopathies. We describe here the onset of the Aicardi–Goutières syndrome, despite the use of ruxolitinib for 10 months, in a patient who had been presymptomatic.

A 4-month-old male infant with biallelic *RNASEH2B* mutations was identified after an older sibling received a diagnosis of the Aicardi–Goutières syndrome. The infant's development had been normal until that time, but he had markers that were suggestive of interferon-signaling activation (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Therefore, when he was 5 months of age, we initiated therapy with ruxolitinib at a

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dose of 5 mg twice daily. When he was 11 months of age, the dose was increased to 7.5 mg twice daily (1 mg per kilogram of body weight per day).

At 12 months of age, the patient's neurologic status remained normal. At 13 months of age, he had weekly fevers. Ruxolitinib was discontinued twice, for 3 days on each occasion, in the 14th month of life. His immunization history included the administration of hepatitis A vaccine at 13 months of age (see the Supplementary Appendix). At 15 months of age, up to which time his neurologic status was normal, he had an abrupt onset of irritability and neurologic deterioration. At 17 months of age, he had spastic–dystonic tetraparesis and was no longer able to speak.

We observed that the concentration of ruxolitinib in the patient's cerebrospinal fluid (CSF) was approximately 10% of that in the plasma; a similar finding was observed in three other patients with the Aicardi–Goutières syndrome (Table S1). Better penetration into the central nervous system or combination therapy[5] might have prevented disease manifestation.

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Figure 1 (next page). Interferon-Signaling Gene (ISG) Expression Scores in the Context of Infection and Vaccination and Aicardi–Goutières Syndrome Scores in Patients Treated with Baricitinib.

In our study, one patient with homozygous *RNASEH2B* mutations had elevated ISG scores after influenza vaccination, which had been administered hours before the sample was obtained, and during a viral illness with fever (Panel A, left graph). Control values (from patients without interferonopathy) are shown in the right graph. In a different cohort,[1] a patient who had the Aicardi–Goutières syndrome with homozygous *SAMHD1* deletions had a decrease in ISG scores and improved clinical findings during baricitinib therapy (Panel B, left graph). During the study, the patient had three infections (a proteus urinary tract infection [UTI], sinusitis, and strep throat), which were treated with antibiotic agents and were associated with elevated ISG scores. Control values (from patients without interferonopathy or with CANDLE [chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures] or SAVI [stimulator of interferon genes–associated vasculopathy with onset in infancy]) are shown in the right graph. The specific methods for assessing the ISG scores shown in Panels A and B varied between the two study cohorts[1,2]; in both cases, higher scores indicate greater interferon signaling. In an additional patient, baricitinib therapy was interrupted owing to concerns with infection (Panel C). Subsequently, neurologic skills, as measured by the Aicardi–Goutières syndrome scale (on which scores range from 0 to 11, with increased scores indicating discrete milestones gained),[3] were lost. Evaluation of developmental milestones, assessed according to the Aicardi–Goutières syndrome scale, is shown for two sibling pairs in our study (Panel D); shown are scores from before treatment, the baseline visit at the initiation of baricitinib treatment, and the last available scores. The older siblings (red) met developmental milestones while they were receiving baricitinib, and the younger siblings (blue) met age-appropriate development milestones as of the last evaluation. Asterisks indicate the initiation of baricitinib therapy.

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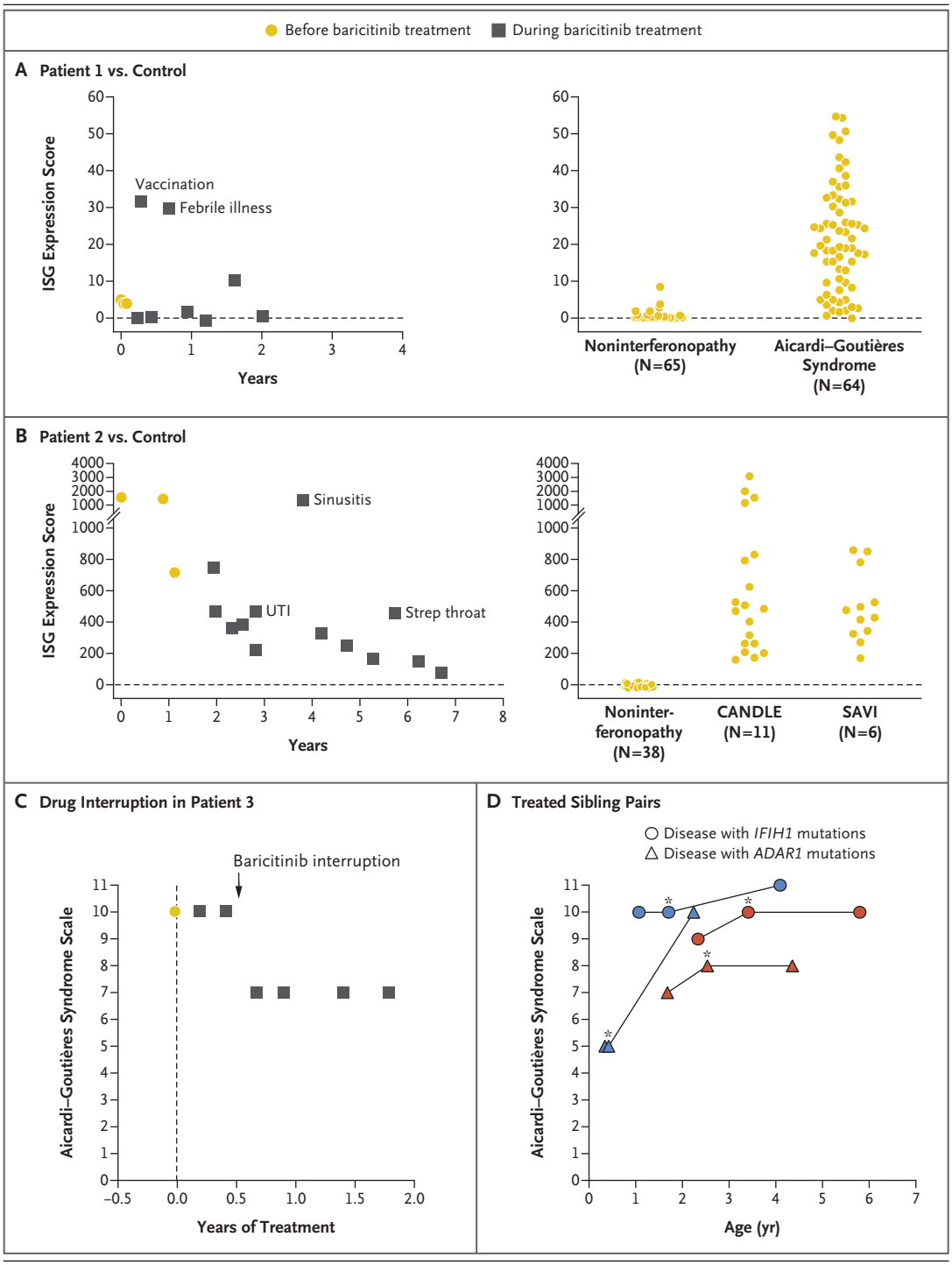

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THE AUTHORS AND A COLLEAGUE REPLY: The Aicardi–Goutières syndrome is a disease of persistent interferon dysregulation. Neven et al. point to the importance of identifying potential disease triggers. Across two separate cohorts of patients who had interferonopathies treated with baricitinib (from our study and from a study by Montealegre Sanchez et al.[1]), there are examples of patients with the Aicardi–Goutières syndrome who had scores indicating elevated interferon-signaling gene (ISG) expression related to environmental factors, such as infection and vaccination (Fig. 1A and 1B).

In addition, early and uninterrupted treatment with JAK inhibitors may be important. In one patient in our study, baricitinib therapy was interrupted for 2 days because of infection concerns, and the dose was subsequently reduced. While baricitinib was not being administered, this patient lost neurologic skills, which have not been regained despite resumption of the dose (Fig. 1C). Two patients in our study had younger siblings who had early symptoms — one with toe walking, and the other with torticollis — and who were treated with baricitinib (Fig. 1D). To date, with baricitinib therapy, the younger siblings have met age-appropriate milestones without regression. We did not assess CSF pharmacokinetics in our study.

The Aicardi–Goutières syndrome is a disease of fluctuating interferon dysregulation, which can be exacerbated by environmental factors. Although there are gaps in knowledge regarding dose levels, target engagement, CSF penetration, environmental risk factors, and the comparison of different JAK inhibitors, our work suggests that early identification and consistent treatment with JAK inhibitors may positively affect neurologic outcomes in patients with the Aicardi–Goutières syndrome.

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